"A STUDY ON HELICOBACTER PYLORI INFECTION IN FIRST DEGREE RELATIVES OF CARCINOMA STOMACH PATIENTS"

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CERTIFICATE

This is to certify that this dissertation entitled **"A study on Helicobacter pylori infection in first degree relatives of carcinoma stomach patients"** submitted by **Dr.Jayakumar Jayakrishnan** to the Faculty of Medical Gastroenterology, The Tamilnadu Dr.MGR Medical University, Guindy, Chennai-600032, in partial fulfillment of the requirement for the award of DM Degree, Branch IV (Medical Gastroenterology) is a bonafide work carried out by him under my direct supervision and guidance.

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CONTENTS

A STUDY ON HELICOBACTER PYLORI INFECTION IN FIRST DEGREE RELATIVES OF CARCINOMA STOMACH PATIENTS

INTRODUCTION

INTRODUCTION

The relationship between Helicobacter pylori and gastric carcinoma is well documented. Therefore, Helicobacter pylori has been designated as a definite carcinogen by the IARC (International Agency for Research on Cancer) which is a branch of the WHO (World Health Organization).

Epidemiological studies show that the H.pylori infected persons have a greater risk of developing gastric adenocarcinoma.[(1)] In 2001, an analysis of 12 studies involving gastric cancinoma and H.pylori estimated that there was a six times increased risk in the development of adenocarcinoma in the non-cardia regions of the stomach for persons infected with H.pylori than those who were not infected.[(2)]

The intestinal type of gastric carcinoma is thought to occur due to environmental causes such as H.pylori infection. However, the diffuse gastric cancer is thought to occur due to a primary genetic cause. Allocating values to the genetic and the environmental contributions in the developing of the intestinal type of gastric carcinoma is difficult since familial clustering is also seen in H.pylori.

10% of the total gastric cancer cases demonstrate familial clustering.[3] Therefore, family history of gastric malignancy can be considered an independent risk factor by itself for the development of gastric carcinoma in spite of adequate H.pylori control.

Genetic factors that play a role in the immune response of a person to H.pylori infection may be responsible for the familial clustering of gastric carcinoma patients (intestinal type).

The development of atrophic gastritis has been associated to a strong immune response involving the Th1 cells. This led to the postulation of the theory that the genes responsible for disease susceptibility in both gastric carcinoma as well as atrophic gastritis may also participate in the immune response to Helicobacter pylori infection.

Uemura et al conducted a study in a set of patients with early gastric cancer who underwent EMR.[4] These patients were distributed into two groups. In the group which received anti-H.pylori treatment following EMR, none developed secondary gastric carcinoma. But in the group that did not undergo H.pylori eradication, 9% of them went on to later develop secondary gastric carcinoma. This study demonstrated that treating Helicobacter pylori infection may prevent development of

secondary gastric carcinoma and therefore should be done in persons who undergo EMR for early gastric carcinoma.

Due to the hereditary risk for gastric carcinoma in first degree relatives of patients with gastric cancer, eradication of H.pylori may help avoid one of the factors that potentiate the risk of developing gastric carcinoma.

Eradication of H.pylori infection can result in many physiologic effects that may decrease the risk of developing gastric carcinoma. The effects are a reduced cell turnover, increased gastric acid secretory capacity, eliminating DNA damage by reducing the reactive oxygen species and restoring ascorbic acid secretion into the gastric secretions.

But concrete evidence proving that eradication of Helicobacter pylori has a protective effect from the development of gastric carcinoma in the form of well-designed clinical studies remains less.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Gastric carcinoma is the second leading cause of mortality due to cancer globally. There is a large geographical variation in incidence of gastric carcinoma with the lowest incidence being seen in South Asia, North America, North Africa and Australia.

EPIDEMIOLOGY

In India, gastric carcinoma ranks fifth among cancer seen in males and seventh among cancer seen in females. The age-adjusted rate (AAR) of gastric cancer among urban registries in India is 3.0–13.2 compared to the worldwide AAR (4.1–95.5). [10]

The worldwide decline in the incidence of gastric cancer has been attributed to an improvement in food hygiene, sanitation and techniques of food preservation. But, this decline in incidence is not seen in certain regions of India.[11] This regional variation in incidence and presentation is reflected in the fact that gastric cancer in South Indian males is found to be more common and occurs almost a decade before their North Indian counterparts.[12]

In India, the highest incidence of gastric carcinoma is seen in Mizoram.[13] The AAR rate of stomach cancer in India as per the National

Cancer Registry had the highest value in Chennai of 11.1 per 100,000 for males and 5.4 in females.

Differences in some dietary pattern and use of tobacco and alcohol are considered as potential risk factors. In a case–control study from Trivandrum, a high intake of rice and chilli along with consumption of high-temperature food were identified as independent risk factors for developing gastric malignancy.[14] In a study conducted at Hyderabad, comparing 94 gastric cancer patients and 100 normal matched controls, smoking ($P<0.01$) and alcohol ($P<0.05$) were found to be significantly associated with gastric carcinoma.[15]

High prevalence of gastric carcinoma in Mizoram has been attributed to dietary and possibly some unknown genetic differences. In a case–control study from Mizoram, the risk of stomach cancer was much higher in current smokers from among the cases.[16] In another study from Chennai, alcohol consumption and eating pickled food were identified as independent risk factors for gastric carcinoma.[17]

ETIOPATHOGENESIS

The most common location of the tumor was in the body of stomach (40.7%) followed by the pylorus (35.5%). Gastric carcinoma can

be classified as either intestinal or diffuse as suggested by Lauren *et al*. based on histological findings.[18] Gastric carcinoma is also classified according to the anatomic site as proximal (cardia, fundus, and GE junction) or distal (pylorus). Incidence of proximal gastric cancers is increasing in the developed world along with an increase in esophageal cancers suggesting that both these entities might have similar risk factors and pathologies.

H.pylori is thought to cause distal gastric cancers and that the overall decline in gastric cancers and more specifically distal cancers worldwide is thought to be due to the reduction or eradication of H.pylori infection due to improved sanitation.[19] Therefore, it is thought that countries that have a very high prevalence of h.pylori should have the most incidence of gastric carcinoma. However this isn't true, as Asia and Africa have high incidences of Helicobacter pylori infection but a low incidence of gastric carcinoma. This paradox suggests that H.pylori by itself cannot cause gastric cancer and a combination of other factors is needed for gastric carcinoma to develop.[20]

Various definite factors that place a person at risk for developing gastric carcinoma are H.pylori infection, chronic atrophic gastritis, intestinal metaplasia, dysplasia, adenomatous gastric polyps, cigarette

smoking, H/O gastric surgery, genetic factors, family H/O gastric cancer (first-degree relatives), FAP with fundic gland polyps, HNPCC, Peutz-Jeghers syndrome and juvenile polyposis.

MICROBIOLOGY

Helicobacter pylori is a gram-negative microaerophilic bacterium that has been identified as the primary aetiologic agent for gastric carcinoma. H.pylori has been designated as a definite carcinogen by the International Agency for Research on Cancer (IARC).

Helicobacter pylori are unique bacteria that are suited to live in the acidic environment present in the human stomach. The spiral shape along with the multiple unipolar flagella of the organism allows it to move in a free manner through the gastric mucous layer, where it may stay protected from low gastric pH.[21] They produce huge amounts of urease which is an enzyme that hydrolyzes urea to alkaline ammonia and CO_2.

EPIDEMIOLOGY OF H.PYLORI

In developing countries, most children are infected by 10 years and spontaneous elimination and subsequent reinfection are common in childhood. This infection may persist into adulthood and therefore prevalence of Helicobacter pylori in the developing countries reaches

>80%. Serological evidence of H.pylori is almost nil in children below 10 years, but increases to 10% in adults (18-30 years) and further to 50% in people older than 60 years. [22]

Twins who grow up together in the same environment have a greater concordance of Helicobacter pylori status than those twins who grow up separately.

Person to person bacterial transmission from feco-oral, oro-oral or gastro-oral means is the most likely explanation for infection.

PATHOGENESIS

Helicobacter pylori shows strict affinity for gastric mucosa and intestinal epithelium with gastric metaplasia. It does not colonize gastric epithelium with intestinal metaplastic change, as the production of antimicrobial factors select against colonization. Helicobacter pylori very rarely colonize the deeper parts of the gastric glandular mucosa since O-glycans present there impair its growth.[23] H.pylori reduces the secretory leukocyte protease inhibitor (antibacterial molecule) which could prevent the infection from persistence. [24]

Another factor that affects colonization is the receptor expression on the host cells which allow *H. pylori* to bind to Lewis (Le) antigens

expressed by host cells.[25] Specific bacterial gene products, mainly BabA, act as a bacterial ligand for the Leb receptor.[26] Few studies have suggested that the babA2 genotype is more commonly associated with duodenal ulcer and gastric carcinoma.[27]

Helicobacter pylori also binds to the molecular complex of invariant chain and class II HLAs expressed on the gastric epithelial cell surface.[28] The Class II major histocompatibility complex molecules were the first epithelial cell receptors for Helicobacter pylori that were demonstrated to directly affect signaling in host cells. Apoptosis of the host cells is induced when urease binds to the epithelial cells. [29] Recently, the gastric trefoil protein TFF1 has been shown to serve as a receptor for Helicobacter pylori. [30]

The Toll-like receptors are a family of PAMPS (pathogen-associated molecular receptors) that may bind bacterial products and enhance bacterial binding and cell signaling. [31]

After *H. pylori* migrates to the gastric epithelium, it attaches to host cells and may damage them so as to obtain nutrients from the subsequent inflammatory exudate or transudate. The main interaction between the bacteria and gastric epithelium involves a segment of bacterial DNA called the cag pathogenicity island (cag PAI). The genes within the cag

PAI encode proteins that may provide a type IV secretion apparatus (i.e., cagE) that permits bacterial macromolecules to translocate into the host cell (i.e., cagA).[32] H.pylori bearing the cag PAI are associated with increased IL-8 expression as also inflammation in the gastric mucosal biopsy specimens and increased IL-8 expression and apoptosis in vitro.[33]

Superoxide (O_2^-) and nitric oxide (NO), produced by infiltrating neutrophils, in a reaction form peroxynitrite ($ONOO^-$) which is a potent reducing agent as well as an oxidant. Urea is hydrolysed by urease to give carbon dioxide that reacts with peroxynitrate and forms $ONO\text{-}OCO_2$ thereby neutralizing peroxynitrate's bactericidal activity. Urease is said to enhance the nitration potential of $ONOO^-$ thus favoring mutagenesis of host cell DNA.

GIT antibodies are usually IgA, which are adapted for protection of the mucosa and confer protective immunity without activation of the complement cascade. During Helicobacter pylori infection, IgA producing cells increase in number. IgM and IgG may also be detected, along with activated complement.

H.pylori infection may be present throughout the life of the host unless antibiotics intervene in its course. Many bacterial factors such as catalase and urease, antagonize innate responses of the host cell.

NATURAL HISTORY OF H.PYLORI

The natural history of chronic *H. pylori* infection includes the following phenotypes [34]: (1) superficial gastritis (2) duodenal ulcer and (3) gastric ulcer/gastric cancer. *H. pylori*–induced duodenal ulcer patients have an increased gastric acid output and a decreased risk for developing gastric carcinoma. [35]

HELICOBACTER PYLORI AND GASTRIC CARCINOMA

Patients with *H. pylori* associated gastric ulcer have a low gastric acid output, and their ulcers are usually associated with premalignant changes such as atrophic gastritis and intestinal metaplasia. Helicobacter pylori infected patients can develop atrophic gastritis at a rate of 1 to 3% every year.[36] Helicobacter pylori is associated with both the intestinal and diffuse-types of adenocarcinomas.

The higher risk of developing gastric adenocarcinoma secondary to *H. pylori* infection depends on many factors such as the strain of bacteria, duration of infection, host genetic factors along with the absence/presence of other factors such as poor diet, smoking, etc.

In a Japanese study that included 1526 persons with PUD, gastric hyperplasia and non-ulcer dyspepsia, only Helicobacter pylori infected

persons developed gastric adenocarcinoma on follow-up ($P < 0.001$).[37] In the West, this association between *H. pylori* and gastric carcinoma seems to be restricted to tumors not involving the cardia.[38]

A combination of a genetically permissive host, a virulent bacterial strain and a favorable environment in the stomach are required for gastric cancer to develop. However, the most important factor appears to be the inducing of chronic inflammation by *H. pylori*. Many carcinogens have been implicated including oxygen free radicals (that can damage DNA), increased $CD4^+$ T cells as well as myeloid cells and also increased production of proinflammatory cytokines. These lead to increased cell turnover, decreased apoptosis and increase the potential for incomplete or faulty DNA repair.[39] Thus, current evidence indicates that the host immune response is the most significant cofactor that can induce development of H.pylori related disease.

Prolonged inflammation is required for the disease to progress via atrophy to gastric carcinoma. Studying the mechanisms of H.pylori related disease is difficult in humans and much of our understanding of the immune response to *Helicobacter* organisms is from the work done on mouse models.

Observations in mouse models laid the path for the conduction of studies in humans which were done in Latin America and Africa. These studies confirmed that those areas with low gastric carcinoma incidence had a higher Th2 when compared with Th1 immune responses to Helicobacter pylori.[40] In areas where intestinal helminths were present in more than 50% of the population and serum IgE levels were elevated, an increased Th2-type response was found.

Diverse genetic variations are seen between different strains of *H. pylori* due to base-pair substitutions within its genome, deletions, insertions and point mutations. Inspite of this genetic diversity, many genes have been identified as risk factors for gastric cancer, such as the *cag* PAI, the *babA2* gene along with the *vacA* gene.

The *H. pylori* genome contains 1.65 million base pairs and codes for nearly 1500 genes. Biological roles have been identified for two-thirds of these genes while the roles played by rest of the one-third of the genome is unknown. [41]

Motility of H.pylori towards the gastric epithelial cells is ensured by many factors, including its spiraling movement (FlaA and FlaB proteins), that help the organism to move through the thick gastric mucus and decrease its viscosity permitting penetration of bacteria.[42]

H. pylori also expresses many genes that help to buffer gastric acid so as to maintain a relatively neutral pH. One of these is the urease gene cluster which is made up of 7 genes, of which UreA/UreB complex (urease enzyme) codes for nearly ten percent of *H. pylori* protein and is necessary for the survival of the bacteria.

Most of *H. pylori* organisms are found on the gastric mucosal cell surface. Some *H. pylori* can be seen within the cell, mainly in premalignant and malignant lesions.(43) Bacterial adherence to the gastric epithelial layer is helped by a family of 32 related outer-membrane proteins (Hop proteins) that include adhesins. BabA is an adhesin encoded by the strain-specific gene *babA2*. BabA binds to the fucosylated Lewis B blood group antigen on the gastric epithelial cells to form a scaffold apparatus that permits the bacterial proteins to enter host epithelial cells. Helicobacter pylori strains possessing the *babA2* gene show tight adherence to epithelial cells and promote an aggressive phenotype that is associated with a higher incidence of gastric adenocarcinoma.(44)

The *cag* PAI is about 40 kb and contains 31 genes. *CagA*, the terminal gene of this island, is used as a marker for the entire *cag* locus.

The cag-positive (cagA+) strains are associated with greater degrees of atrophic changes, more severe inflammation, and a higher risk for progression to gastric adenocarcinoma.(45)

CagA could directly promote transformation, growth and migration. Other genes within the PAI may be important for development of disease as they may be necessary in vitro epithelial cell cytokine release, but they dont appear to have sa great an effect on immune cell cytokine activation as *cagA*. (46) This can explain the attenuated inflammatory response and the decreased risk of cancer seen with cagA− strains in vivo.(47)

All the strains of *H. pylori* carry the *vacA* gene that codes for a pore-forming vacuolating toxin. However, the expression of vacA can differ depending on allelic variation. Nearly 50% of *H. pylori* strains express the vacA protein, which inhibits T cell activation in vitro.(48) Though *cagA* and *vacA* map to different loci within the Helicobacter pylori genome, the vacA protein is commonly expressed in cagA+ strains. “Virulent strains” (cagA+, cagE+, and VacA+ s1m1) seem to induce the proinflammatory mediators much more than the “nonvirulent strains” (cagA−, cagE−, and VacA−). This can explain the high association of cagA+ strains with gastric carcinoma.

INVESTIGATIONS FOR H.PYLORI

The American College of Gastroenterology (ACG) guidelines recommend tests for *H. pylori* infection only if the physician is ready to treat all patients who test positive.[49] Asymptomatic persons need not be treated except persons with a family h/o gastric carcinoma.

Indications for Testing and Treatment of *Helicobacter pylori* Infection

Supported by evidence

	Active peptic ulcer disease (gastric or duodenal ulcer)
	Confirmed h/o peptic ulcer (not previously treated for *H. pylori*)
	Gastric MALT lymphoma (low grade)
	Following endoscopic resection of early gastric cancer
	Uninvestigated dyspepsia (if *H. pylori* population prevalence high)

Controversial

	Functional dyspepsia
	GERD
	Patients on NSAIDs, especially when initiating NSAID treatment
	Unexplained IDA/ITP
	Populations with increased risk of gastric carcinoma

Diagnosis of Helicobacter pylori may be done by endoscopic as well as non-endoscopic methods. Some techniques directly detect H.pylori such as histologic demonstration of H.pylori, detection of bacterial antigen in the stool & culture of the organism. Other methods detect Helicobacter pylori indirectly as in urease tests and evaluation of an antibody response to mark the presence of Helicobacter pylori by serology.[50]

Diagnostic Tests for Helicobacter pylori

During an endoscopic procedure, 3 methods can be used to identify H.pylori.They are the urease test of biopsy specimen, histopathological examination and culture. Urease test of biopsy specimen has been proposed as the initial test of choice since the method is quick, relatively inexpensive, generally accurate and easy to perform. The gastric tissue specimen is tested for activity of urease by putting many bits of tissue in a medium containing pH reagent and urea. Urease produced by H.pylori hydrolyzes urea and liberates ammonia, which produces an alkaline pH and this results in a change in colour of the test medium. The test results can be read in a few minutes to hours. This test is less costly than histological examination. Therefore, a cost-cutting measure is to delay sending tissue for histological examination till urease test results are

available. Urease tests are 95% to 100% specific with false-positive tests being not very common.[51] Accuracy of the urease test can be affected by the presence of blood in the stomach [52] and also recent/current use of drugs such as bismuth-containing compounds, antibiotics or PPIs. [53] Urease test negativity therefore cannot exclude *H. pylori* infection in an individual taking the above medications. Testing biopsy tissues from various regions of the stomach, stopping the offending drug for a few weeks and delayed UGI scopy can improve the sensitivity of the test.

Histopathological examination of the gastric mucosa isn't necessary for the diagnosis of H.pylori. However, this test may provide information about the activity of Helicobacter pylori and mucosal inflammation severity. Histological examination can also detect the presence of metaplasia, dysplasia, and neoplasia. Biopsy of "clinically suspicious" areas, multiple biopsies, taking samples from both the lesser and greater curvatures of gastric antrum as well as the body should be done mainly when searching for atrophic gastritis and/or intestinal metaplasia. Histopathologic exam is the gold standard for confirmation of Helicobacter pylori infection. This test is 95% sensitive and 98% specific.[54] Detecting organisms is better when tissue is processed with special stains like Silver stain, Giemsa stain or Genta stain or specific immune stains.[55]

Helicobacter pylori culture is difficult, since it is very fastidious, grows slowly and requires use of specialized media and a controlled growth environment. When culturing for Helicobacter pylori, the biopsy forceps should not be contaminated with formalin prior to obtaining the tissue specimen. The tissue specimen should be kept in a container that contains a few drops of saline for preservation of the tissue while being transported to the microbiology laboratory. Culture is advised only for persons with refractory disease where identifying sensitivity to antibiotics may help in guiding subsequent treatment.

Nonendoscopic tests are more commonly used in the diagnosis of Helicobacter pylori with serology being the most popular test used. ELISA detects the presence of IgG antibodies to many bacterial antigens seen in the serum. Testing for IgA and IgM class antibodies is unreliable and therefore cannot be recommended. Though serology is cheaper, not invasive and ideal in a primary care setting, its accuracy depends on prevalence of Helicobacter pylori in the population that is being tested. Serology is highly sensitive (90% - 100%) but the specificity varies (76% to 96%), mainly in areas where prevalence of Helicobacter pylori is low. In regions where the prevalence of H.pylori is low, the NPV of serology is high while the PPV is low.[56] Therefore, serology tests that are positive should always be confirmed with any other method like a stool antigen

or urea breath test prior to the start of therapy. Otherwise, it is better to initially go for a test that can detect active Helicobacter pylori infection. After treatment, if a positive serological test becomes negative, it indicates a cure. Even after successful eradication of H.pylori, the serology may remain positive for months to years.[57] Because of this "serologic scar", serology can't be used to confirm eradication of H.pylori after treatment.

The urea breath test detects an active Helicobacter pylori infection and is therefore can be used for making the primary diagnosis, to confirm the accuracy of the serological test as well as the documenting of successful treatment.Urea breath test depends on hydrolysis of orally administered carbon isotope tagged urea (13C or 14C) by Helicobacter pylori. This gives rise to ammonia and tagged CO_2 that is detected in breath samples. Since 13C is a non-radioactive isotope, it is better for use in pregnant women and children. The radiation dose exposure with the 14C test is 1 microCi.[58] UBT has more than 95% specificity and so, false-positive results are not very common. The sensitivity of UBT is 88% -95% with false-negative results seen in those on antisecretory drugs mentioned earlier. Therefore for improving the accuracy of the test, antibiotics shouldn't be given 4 weeks and PPIs for at least 1 week prior

to breath testing.Urea breath test is inaccurate in persons with previous H/O gastric resective surgery.

A stool immunoassay helps detect the bacterial antigens in H.pylori infected patients. This method can be used to diagnose active Helicobacter pylori infection and also to confirm eradication of H.pylori following treatment. The stool test is 94% sensitive and 97% specific and these are comparable with that of the urea breath test. Here too, the sensitivity of stool testing sensitivity can be affected by antibiotics, PPI etc., that may reduce bacterial load. Therefore, precautions similar to those for urea breath test need to be followed while doing the stool tests.[59]

Though PCR is very sensitive for detecting *H. pylori* in gastric tissue biopsies, it isn't practically useful for routine clinical purposes. This test is only used for research purposes for identification of the bacteria when culture may be difficult.[60]

The current recommendations for H.pylori testing are as follows:

The initial test preferred for the diagnosis of Helicobacter pylori is either UBT or a stool antigen assay as they help in the detection of active infection. Serological testing is useful only for exclusion of Helicobacter

pylori infection. Endoscopic biopsy can be done for patients who have an ulcer or MALT lymphoma and also in persons who require a follow-up OGD scopy for gastric ulcer follow-up. Urease testing on tissue biopsy specimens can be done in those not on anti-secretory medications and when histopathological examination is not necessary.

Successful Helicobacter pylori eradication can be confirmed when clinically indicated with either a urea breath test or stool antigen test. However they shouldn't be done earlier than 4-6 weeks following treatment completion as early testing may show false-negative results. Here too, antisecretory drugs should be stopped at least 1 week before testing so as to improve the accuracy. Serology isn't useful for follow-up as it may remain positive in a lot of patients for a few months or sometimes even years after eradication of H.pylori.

TREATMENT OF H.PYLORI

A sequential regimen given for 10 days improved the rate of eradication in comparision with the standard PPI triple therapy (89% vs. 77 %). The drugs given are a Proton Pump Inhibitor and Amoxicillin for the initial five days and then Proton Pump Inhibitor along with clarithromycin and tinidazole for the next five days. A pooled analysis of various studies confirmed that sequential therapy is better, more so in

macrolide-resistant strains.[61] Dual regimens with a solo antibiotic and a Proton Pump Inhibitor are not recommended as the rate of eradication is much lesser than the triple drug regimens.[62]

Bismuth-based therapy, with a combination of a bismuth salt, metronidazole, tetracycline along with a PPI daily for 14 days was one of the first combinations used in the therapy of *H. pylori*. Though it is highly effective with >80% eradication, the large number of tablets and frequent minor side effects has a negative effect on tolerability and compliance. Therefore, this regimen is kept in reserve as either a second-line regimen or a retreatment regimen.[63]

Initial treatment of *H. pylori* infection may fail in up to 25% of patients due to either drug resistance, poor compliance or due to patient factors such as younger age, previous antibiotic use, smoking, and presence of functional dyspepsia.[64] Another “rescue therapy” includes a PPI, levofloxacin , along with amoxicillin for 10 days is approximately 80% effective. Another combination of PPI and amoxicillin, along with rifabutin for 10 days is reportedly effective in 85% patients.

Initially treatment for Helicobacter pylori can be started with a 10- to 14-day course of PPI triple therapy (Proton pump inhibitor, clarithromycin and amoxicillin) but the 10 day sequential regimen can be

an alternative if resistance to clarithromycin is suspected. If infection continues to persist even after the above, retreatment with one of the other PPI triple regimens or a bismuth based regimen is given for 2 weeks. Selecting a treatment regimen on the basis of antibiotic sensitivity is not recommended as a matter of routine.

STUDIES ANALYSING ASSOCIATION OF HELICOBACTER PYLORI AND GASTRIC PREMALIGNANT CHANGES IN FIRST DEGREE RELATIVES OF PATIENTS WITH GASTRIC CARCINOMA

In a study by Brenner H et al, they compared the prevalence of H. pylori in subjects with and without parental H/O gastric carcinoma to evaluate the role of Helicobacter pylori in familial aggregation of gastric carcinoma. Totally, 1351 males and females aged between 30 and 74 years were included in the study. The prevalence of Helicobacter pylori was much higher (69%) among those with a parental H/O gastric carcinoma than among the others (44%). These results indicate that familial aggregation of gastric carcinoma can be explained partially by familial clustering of Helicobacter pylori infection.

In another study by El-Omar EM et al, Helicobacter pylori infection, gastric secretory function, and histological examination of stomach were assessed in 100 first-degree relatives of gastric carcinoma patients and compared with controls that did not have family H/O gastric

carcinoma. Relatives of patients with gastric carcinoma had an increased prevalence of premalignant changes, but this was restricted to persons with Helicobacter pylori infection. Therefore, prophylactic H.pylori eradication should be offered to these persons.

In a State of the Art Critique published in The American Journal of Gastroenterology in 2005 by Peter Malfertheiner et al, the conclusion was as follows: “Based on "in depth" evidence presented at this workshop, the majority of the scientific task force favored a search-and-treat strategy in first-degree relatives of gastric cancer patients and an overwhelming majority felt that a more general screen-and-treat strategy should be focused in the first instance in a population that has a high incidence of Helicobacter pylori associated diseases.”

There is a lack of literature available on studies done in this aspect in India. Hence, this study was done to find the prevalence of Helicobacter pylori and assess its impact on gastric premalignant changes in first degree relatives of gastric carcinoma patients.

AIM OF THE STUDY

AIM OF THE STUDY

- To assess the prevalence of gastric Helicobacter pylori infection in first degree relatives of gastric carcinoma patients and compare it with the same in the controls

- To look for presence of premalignant histological changes in the stomach in the above persons

- To look for any association between Helicobacter pylori and presence of premalignant changes in the study subjects

MATERIALS AND METHODS

MATERIALS AND METHODS

This case control study was carried out in the Department of Digestive Health and Diseases, Government Peripheral Hospital, Anna Nagar, Chennai from January 2012 to February 2013.

Approval for the conduct of this study was obtained from the Ethical Committee at Kilpauk Medical College prior to starting the study.

INCLUSION CRITERION

- First degree relative of a gastric carcinoma patient

EXCLUSION CRITERIA

- Presence of peptic ulcer and /or GI bleeding on endoscopy
- Previous H/O gastrectomy
- Presence of any life-threatening condition
- Consumption of PPIs/H2RAs/NSAIDs/Antibiotics 4 weeks prior to endoscopy
- Persons who refused OGD scopy

Patients attending the DDHD, GPH, Anna Nagar, Chennai who had gastric carcinoma were identified and their first degree relatives (siblings or children) listed out.

These persons were then informed about the study and written informed consent was obtained for including them in the study.

From these listed persons, those who had the exclusion criteria were omitted and the rest were included in the study.

This was compared with the control group that had no family H/O gastric carcinoma. These patients were people who reported to our out-patient department for other symptoms. Written informed consent from them also was obtained prior to including them in the study. Those who came under the exclusion criteria were excluded from the study.

After getting a detailed history regarding any complaints, drug intake, surgery and substance abuse, clinical examination of the patient was performed.

Then, the subject was subjected to upper GI endoscopy. Those with any of the findings listed under the exclusion criteria were ruled out from the study.

Finally a total of 100 persons were recruited for this study, 50 in the study group and 50 in the control group.

Both the control and test groups were matched for both age as well as sex.

From every person in the study, multiple biopsies were taken from the stomach as per the Sydney system. A minimum of five tissue specimens were biopsied: two specimens were taken from the antrum within 2 to 3 cm from the pylorus, two from the body about 8 cm from the cardia (one each from the lesser and greater curvatures) and one specimen from the incisura.

One tissue specimen was used for the rapid urease test, wherein a colour change from yellow to various shades of pink within an hour denoted the presence of Helicobacter pylori.

The rest of the tissue specimens were then sent to the Department of Pathology, Kilpauk Medical College for histopathological examination.

The same procedure was also repeated with the subjects in the control group.

The results were then tabulated and analysed.

Statistical analysis of the data was done using the software SPSS (version 17).

Helicotec-UT (Rapid urease test)

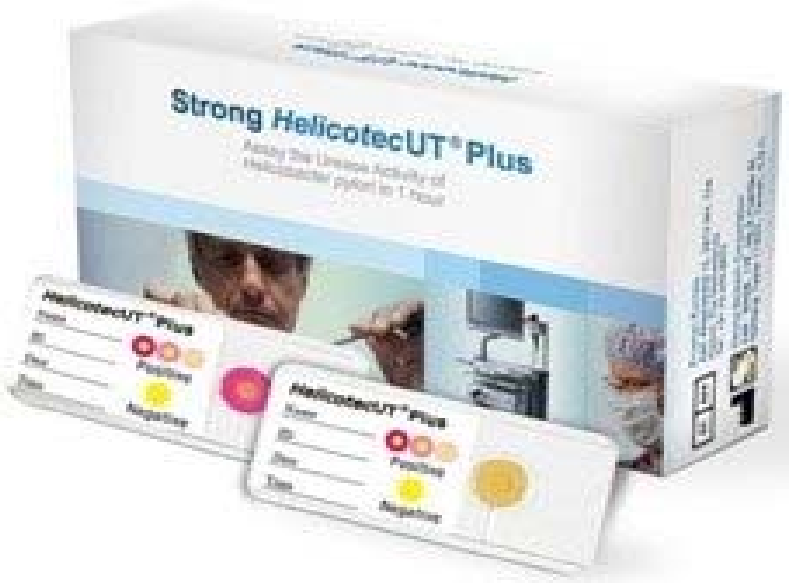
Helicotec-UT is a slide test designed to detect Helicobacter pylori by the presence of its urease activity in gastric mucosal biopsy specimens. Helicobacter pylori produce large amounts of urease which hydrolyze urea into ammonium ion and bicarbonate.

When the tissue specimen of a patient is immersed in the Helicotec-UT test gel and observed over a period of time, the elevated pH caused by the activity of urease is demonstrated by a colour change of the pH indicator in the test gel.

The pre-test gel is yellow in colour. If the colour changes to pink after placing the tissue specimen in the gel, the test is positive for H.pylori. If the gel remains yellow in colour, then the test is negative for H.pylori.

RAPID UREASE TEST KIT USED IN THIS STUDY-

HelicotecUT® PLUS



RESULTS AND STATISTICAL ANALYSIS

RESULTS AND STATISTICAL ANALYSIS

A total of 100 persons were recruited for this study.

50 persons who were first degree relatives of patients with gastric carcinoma formed the study group after applying the exclusion criteria.

50 persons who presented to our department with other complaints were recruited for the study to act as controls after obtaining their consent.

Statistical analysis was done using independent sampling T-test for analysis of age whereas the chi square test was used for the rest of the parameters using the SPSS software (Version 17).

The levels of the P-value and its significance are as follows:

1) P-value of 0.000 to 0.010 indicates that the data correlation is significant at the 1 % level (denoted by **)

2) P-value of 0.010 to 0.050 indicates that the data correlation is significant at the 5 % level (denoted by *)

3) P-value of 0.051 to 1.000 indicates that it is not statistically significant at the 5% level

4) P-value = 0.000 indicates high statistical significance (denoted by <0.001 **)

Both the study group and control group were found to match for age by the T-test and for the gender by the chi-square test.

Both the groups were matched for age (p=0.856).

In the study group, there were 31 males and 19 females whereas there were 30 males and 20 females in the control group (p=0.838).

There were a total of 45 alcoholics (24 in the study group and 21 in the control group). Association between alcohol and prevalence of Helicobacter pylori was statistically significant in both the study and control groups.

There were a total of 49 smokers (26 in the study group and 23 in the control group). Association between smoking and prevalence of H.pylori was statistically significant in the control group but was not significant in the study group.

There were a total of 37 tobacco chewers (20 in the study group and 17 in the control group).). Association between tobacco chewing and prevalence of Helicobacter pylori was statistically significant in both the study and control groups.

Significantly, none of the female subjects were either alcoholics or smokers.

In the control group, the rapid urease test was positive in 29 persons (18 males and 11 females), whereas it was positive in 39 persons (25 males and 14 females) in the study group (p=0.032*).

The prevalence of Helicobacter pylori among males was 81% in the study group whereas it was 60% in the control group.

The prevalence of Helicobacter pylori among females was 74% in the study group whereas it was 55% in the control group.

In the control group, histological examination revealed Helicobacter pylori in 25 persons (15 males and 10 females), whereas it was positive in 34 persons (22 males and 12 females) in the study group (p= 0.067).

In the control group, 25 out of the 29 persons (86%) who showed a positive rapid urease test also showed the bacteria on histological examination. But 4 (14%) persons with a positive rapid urease test failed to demonstrate the histological presence of Helicobacter pylori (p=0.000).

In the study group, , 34 out of the 39 persons (87%) who had a positive rapid urease test showed the bacteria on histological examination. But 5 (13%) persons with a positive rapid urease test failed to demonstrate the histological presence of Helicobacter pylori (p=0.000).

But in both the groups, all those persons who demonstrated Helicobacter pylori histologically were positive for the rapid urease test.

Premalignant changes in the stomach were seen only in 4 persons- all of them in the study group only (p= 0.268). The only premalignant change seen in our study was atrophic gastritis. Intestinal metaplasia and dysplastic changes in the stomach were not seen in our study.

The significant factor here was the occurrence of premalignant changes only in those persons who tested positive for Helicobacter pylori.

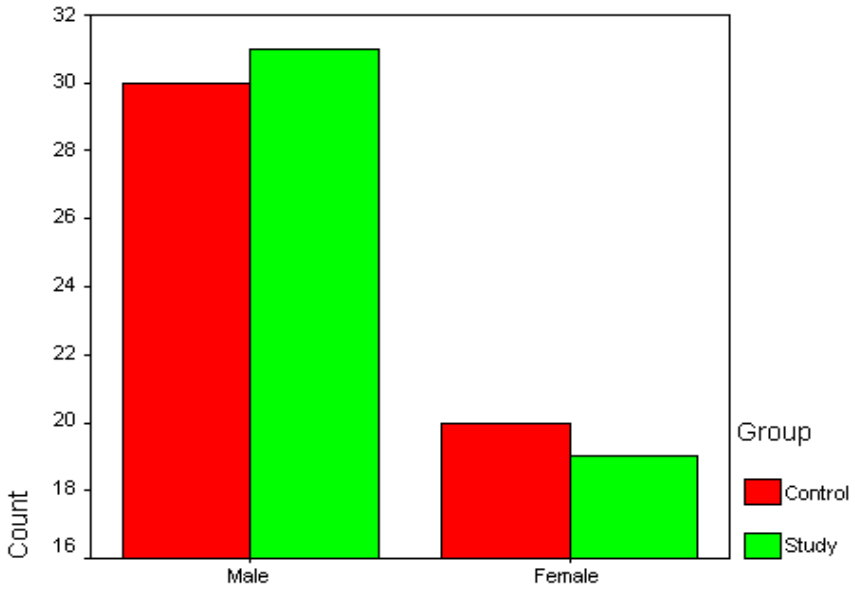
AGE

	Group	N	Mean	Std. Deviation	Std. Error Mean
Age in years	Control	50	36.14	11.148	1.577
	Study	50	35.74	10.795	1.527

	t-test for Equality of Means						
	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
						Lower	Upper
Age in years	.182	98	.856	.40	2.195	-3.955	4.755
	.182	97.898	.856	.40	2.195	-3.955	4.755

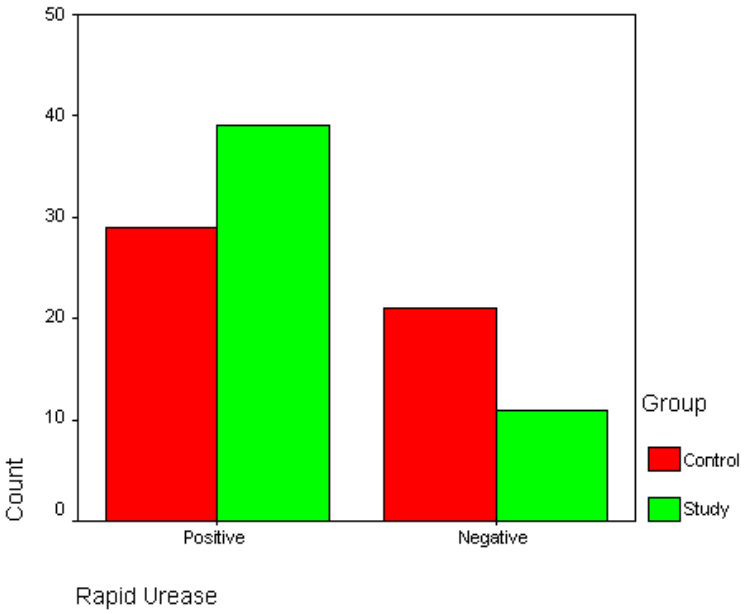
SEX

			Group		Total	P value
			Control	Study		
Sex	Male	Count	30	31	61	0.838
		% within Sex	49.2%	50.8%	100.0%	
		% within Group	60.0%	62.0%	61.0%	
	Female	Count	20	19	39	
		% within Sex	51.3%	48.7%	100.0%	
		% within Group	40.0%	38.0%	39.0%	
Total		Count	50	50	100	
		% within Sex	50.0%	50.0%	100.0%	
		% within Group	100.0%	100.0%	100.0%	



RAPID UREASE TEST

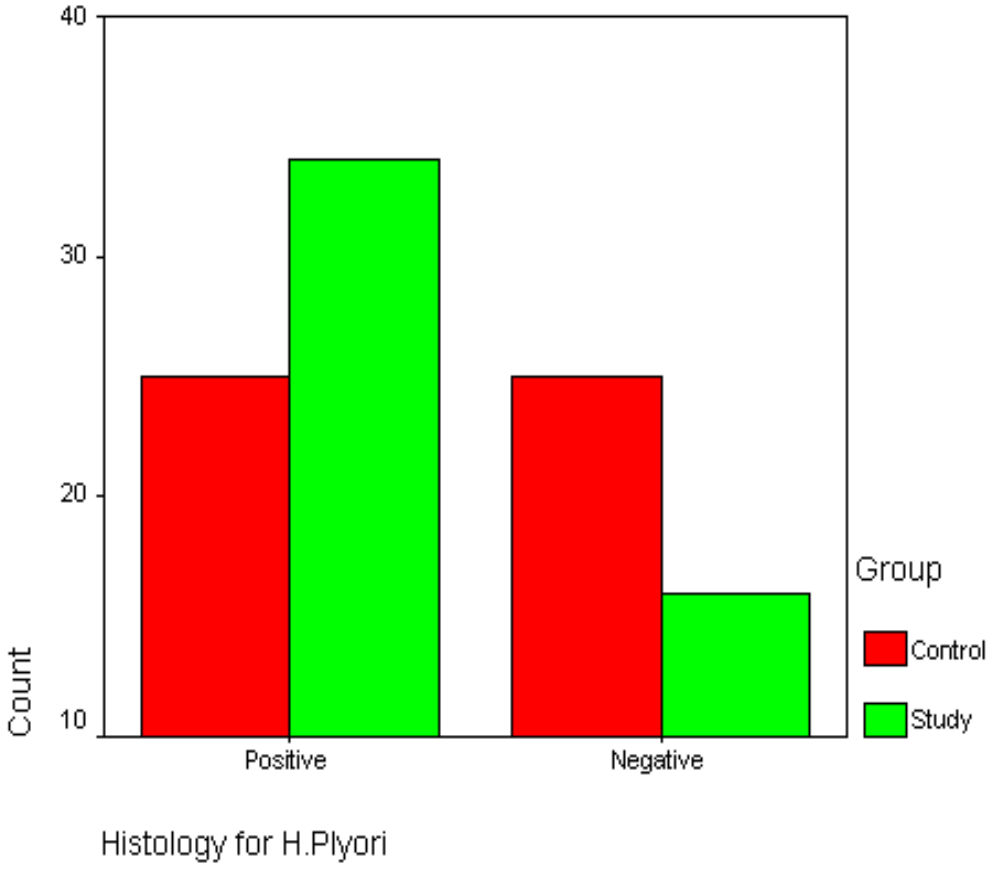
			Group		Total	
			Control	Study		P value
Rapid Urease	Positive	Count	29	39	68	
		% within Rapid Urease	42.6%	57.4%	100.0%	
		% within Group	58.0%	78.0%	68.0%	
	Negative	Count	21	11	32	
		% within Rapid Urease	65.6%	34.4%	100.0%	0.032*
		% within Group	42.0%	22.0%	32.0%	
Total		Count	50	50	100	
		% within Rapid Urease	50.0%	50.0%	100.0%	
		% within Group	100.0%	100.0 %	100.0%	



HISTOLOGY FOR H.PYLORI

			Group		Total	
			Control	Study		P value
Histology for H.Plyori	Positive	Count	25	34	59	
		% within Histology for H.Plyori	42.4%	57.6%	100.0%	
		% within Group	50.0%	68.0%	59.0%	
	Negative	Count	25	16	41	
		% within Histology for H.Plyori	61.0%	39.0%	100.0%	0.067
		% within Group	50.0%	32.0%	41.0%	
Total		Count	50	50	100	
		% within Histology for H.Plyori	50.0%	50.0%	100.0%	
		% within Group	100.0%	100.0%	100.0%	

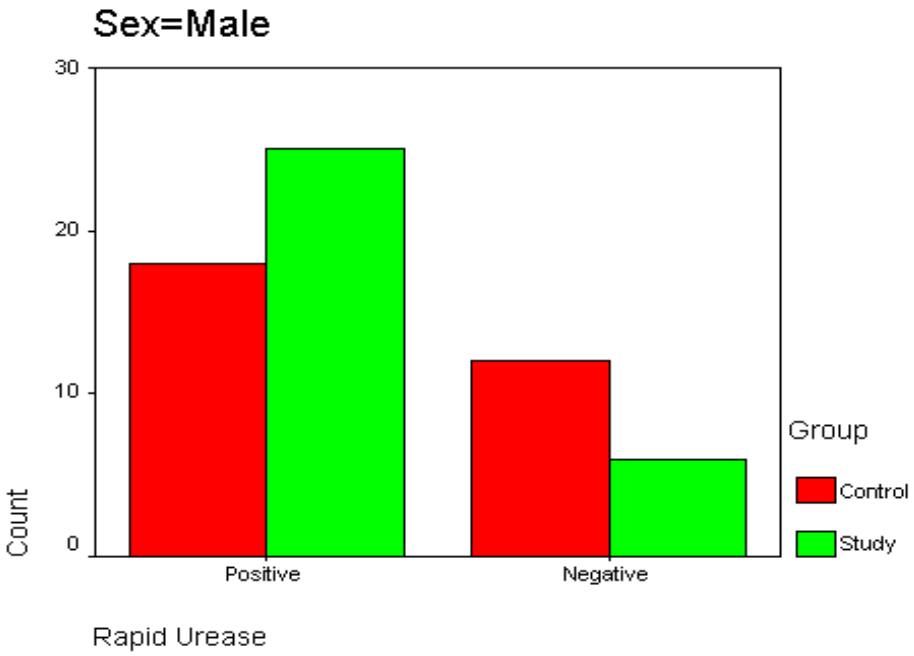
HISTOLOGY FOR H.PYLORI

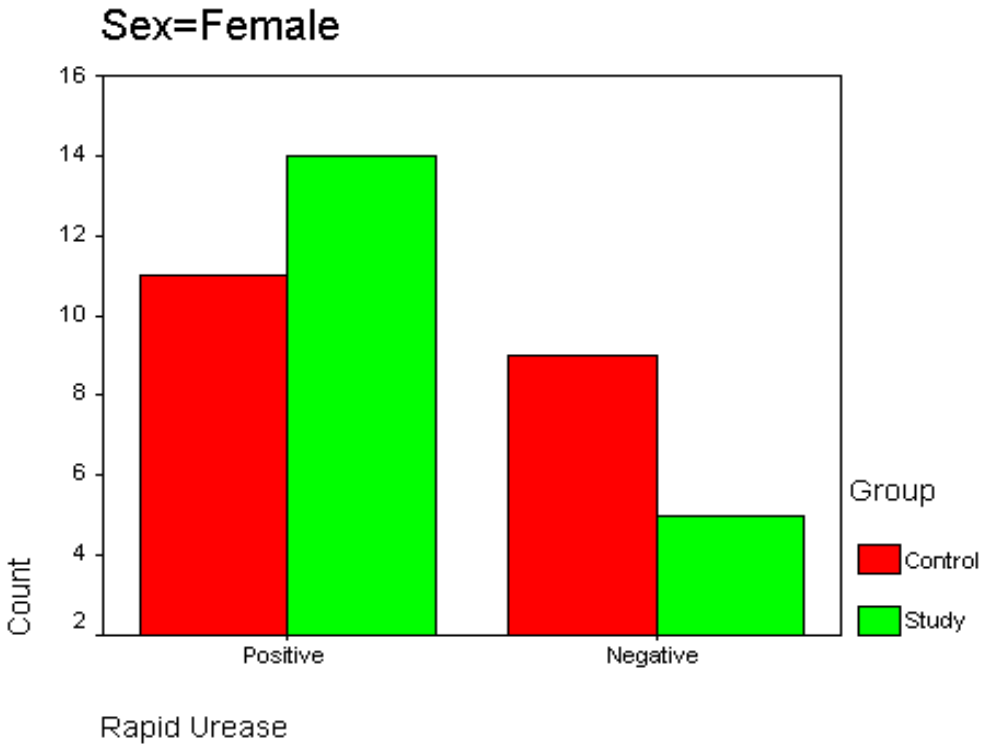


RAPID UREASE TEST VS SEX CROSS TABULATION

Sex				Group		Total	
				Control	Study		P value
Male	Rapid Urease	Positive	Count	18	25	43	
			% within Rapid Urease	41.9%	58.1%	100.0%	
			% within Group	60.0%	80.6%	70.5%	0.77
		Negative	Count	12	6	18	
			% within Rapid Urease	66.7%	33.3%	100.0%	
			% within Group	40.0%	19.4%	29.5%	
	Total		Count	30	31	61	
			% within Rapid Urease	49.2%	50.8%	100.0%	
			% within Group	100.0%	100.0%	100.0%	
Female	Rapid Urease	Positive	Count	11	14	25	
			% within Rapid Urease	44.0%	56.0%	100.0%	
			% within Group	55.0%	73.7%	64.1%	
		Negative	Count	9	5	14	0.224
			% within Rapid Urease	64.3%	35.7%	100.0%	
			% within Group	45.0%	26.3%	35.9%	
	Total		Count	20	19	39	
			% within Rapid Urease	51.3%	48.7%	100.0%	
			% within Group	100.0%	100.0%	100.0%	

RAPID UREASE TEST VS SEX CROSS TABULATION

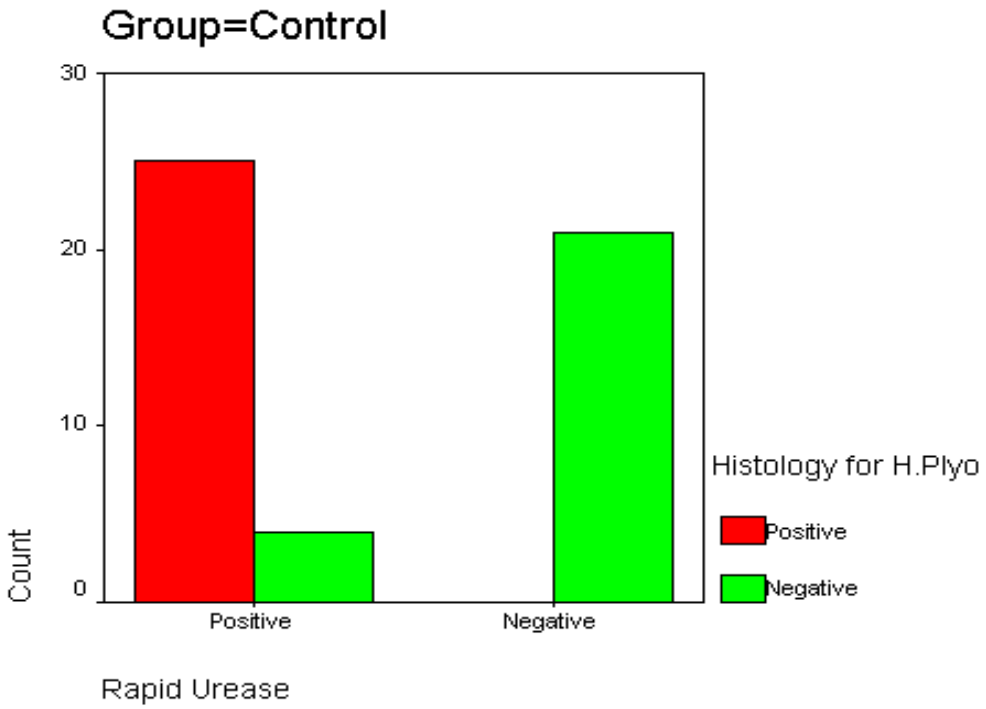


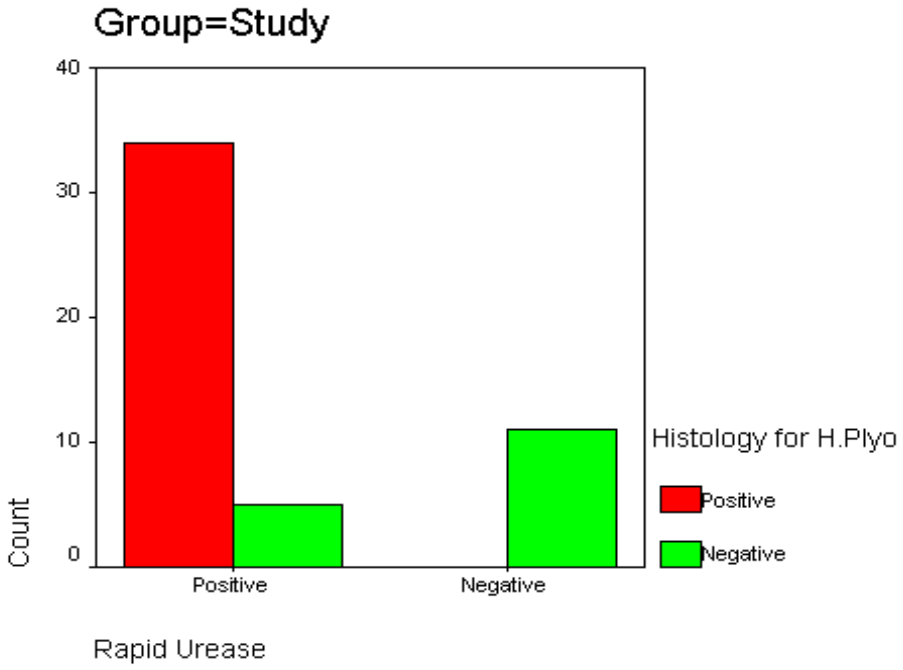


RAPID UREASE VS HISTOLOGY FOR H.PYLORI

Group				**Histology for H.Plyori**		**Total**	
				Positive	**Negative**		**P value**
Control	Rapid Urease	Positive	Count	25	4	29	<0.001** (for both control and study groups)
			% within Rapid Urease	86.2%	13.8%	100.0%	
			% within Histology for H.Plyori	100.0%	16.0%	58.0%	
		Negative	Count	0	21	21	
			% within Rapid Urease	.0%	100.0%	100.0%	
			% within Histology for H.Plyori	.0%	84.0%	42.0%	
	Total		Count	25	25	50	
			% within Rapid Urease	50.0%	50.0%	100.0%	
			% within Histology for H.Plyori	100.0%	100.0%	100.0%	
Study	Rapid Urease	Positive	Count	34	5	39	
			% within Rapid Urease	87.2%	12.8%	100.0%	
			% within Histology for H.Plyori	100.0%	31.3%	78.0%	
		Negative	Count	0	11	11	
			% within Rapid Urease	.0%	100.0%	100.0%	
			% within Histology for H.Plyori	.0%	68.8%	22.0%	
	Total		Count	34	16	50	
			% within Rapid Urease	68.0%	32.0%	100.0%	
			% within Histology for H.Plyori	100.0%	100.0%	100.0%	

RAPID UREASE VS HISTOLOGY FOR H.PYLORI

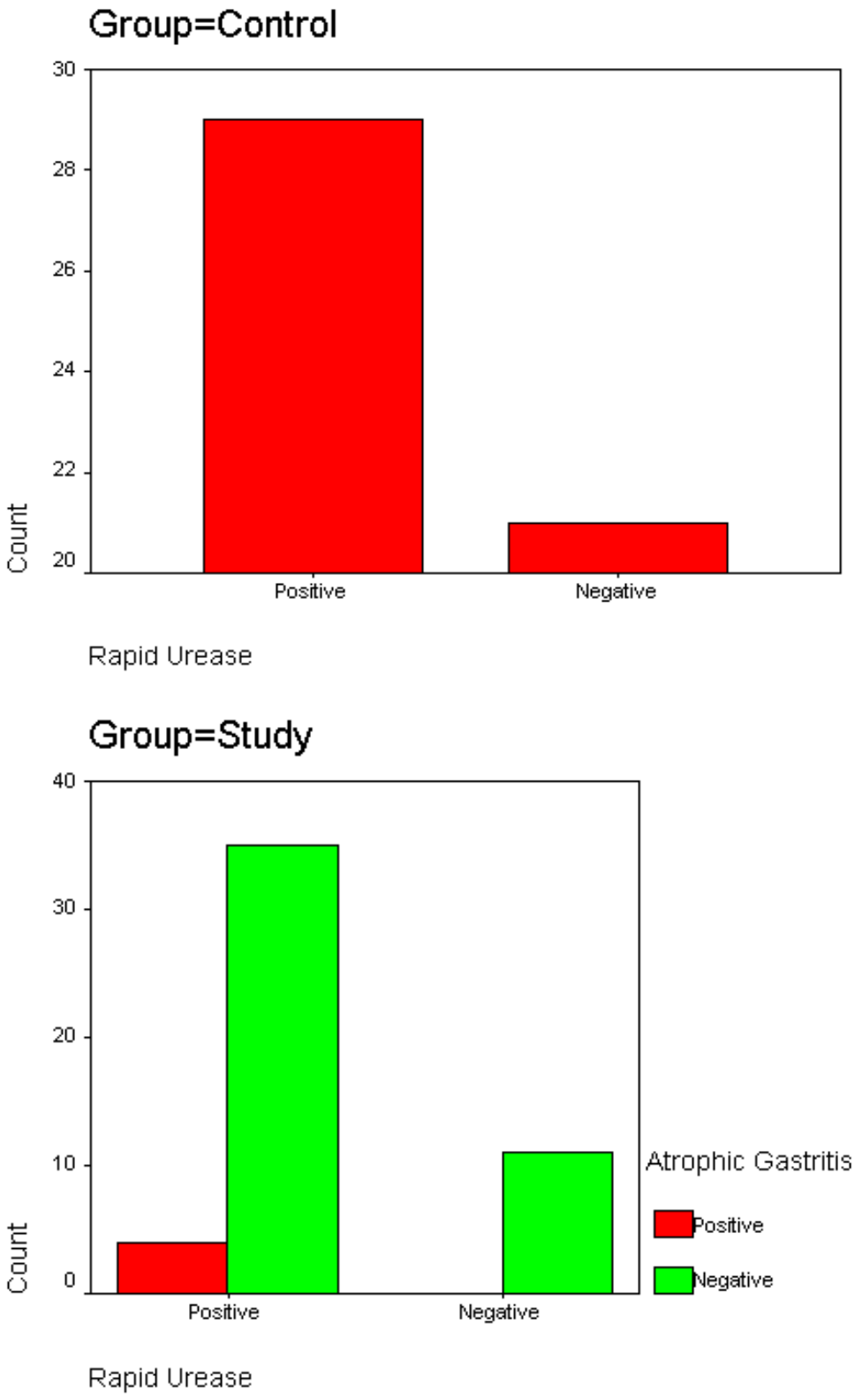




RAPID UREASE VS PREMALIGNANT CHANGES

Group				Atrophic Gastritis		Total	
				Positive	Negative		P value
Control	Rapid Urease	Positive	Count		29	29	
			% within Rapid Urease		100.0%	100.0%	
			% within Atrophic Gastritis		58.0%	58.0%	
		Negative	Count		21	21	
			% within Rapid Urease		100.0%	100.0%	
			% within Atrophic Gastritis		42.0%	42.0%	
	Total		Count		50	50	
			% within Rapid Urease		100.0%	100.0%	
			% within Atrophic Gastritis		100.0%	100.0%	
Study	Rapid Urease	Positive	Count	4	35	39	
			% within Rapid Urease	10.3%	89.7%	100.0%	
			% within Atrophic Gastritis	100.0%	76.1%	78.0%	0.268
		Negative	Count	0	11	11	
			% within Rapid Urease	.0%	100.0%	100.0%	
			% within Atrophic Gastritis	.0%	23.9%	22.0%	
	Total		Count	4	46	50	
			% within Rapid Urease	8.0%	92.0%	100.0%	
			% within Atrophic Gastritis	100.0%	100.0%	100.0%	

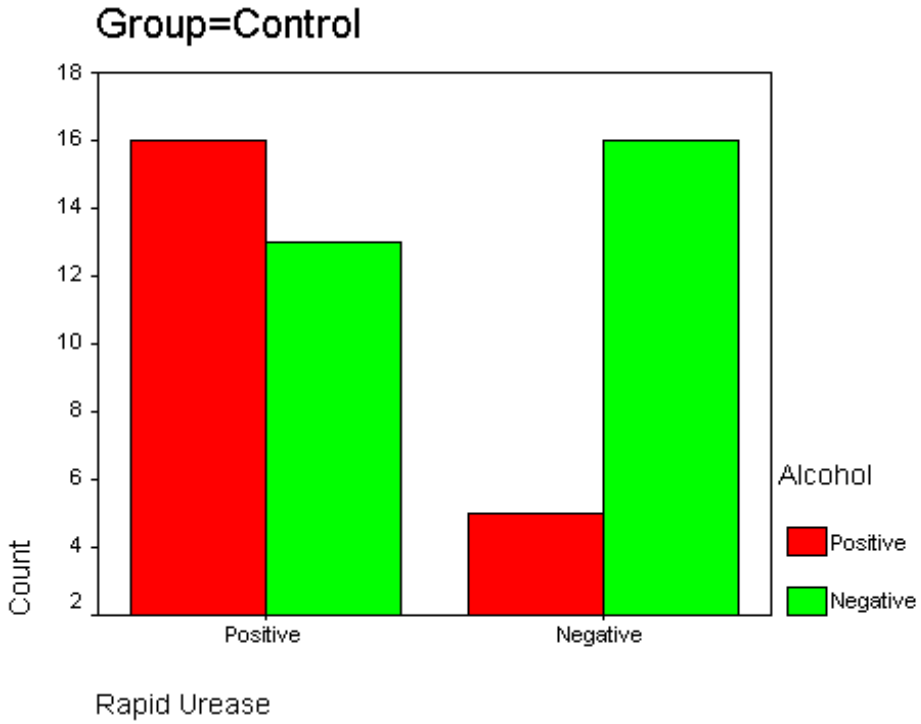
RAPID UREASE VS PREMALIGNANT CHANGES

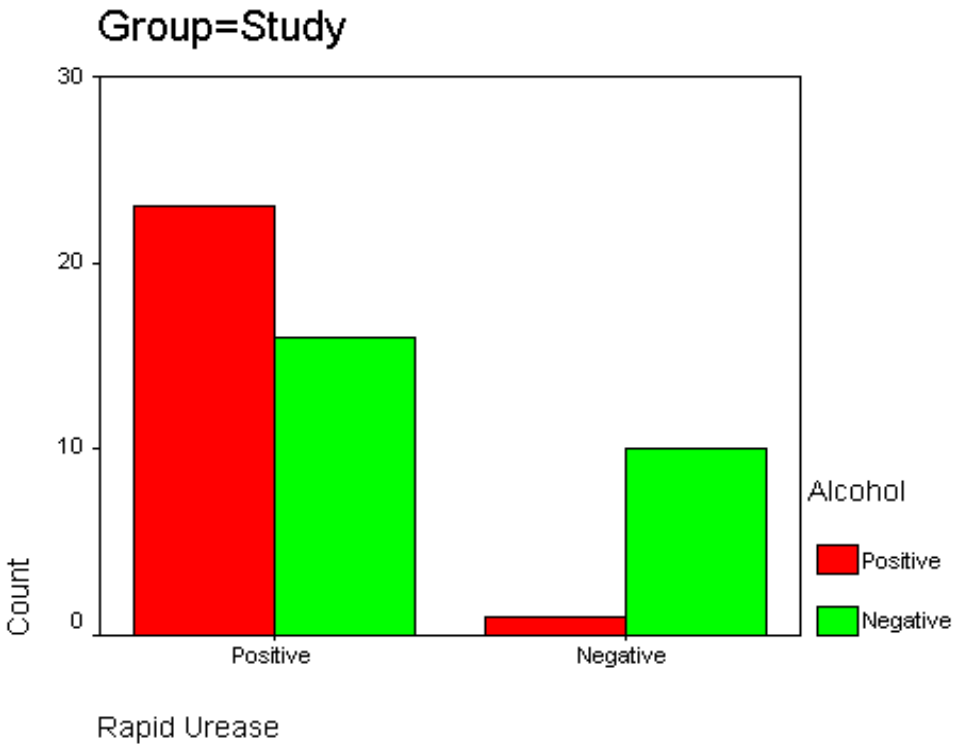


RAPID UREASE * ALCOHOL * GROUP

Group				Alcohol		Total	P value
				Positive	Negative		
Control	Rapid Urease	Positive	Count	16	13	29	0.027*
			% within Rapid Urease	55.2%	44.8%	100.0%	
			% within Alcohol	76.2%	44.8%	58.0%	
		Negative	Count	5	16	21	
			% within Rapid Urease	23.8%	76.2%	100.0%	
			% within Alcohol	23.8%	55.2%	42.0%	
	Total		Count	21	29	50	
			% within Rapid Urease	42.0%	58.0%	100.0%	
			% within Alcohol	100.0%	100.0%	100.0%	0.003**
Study	Rapid Urease	Positive	Count	23	16	39	
			% within Rapid Urease	59.0%	41.0%	100.0%	
			% within Alcohol	95.8%	61.5%	78.0%	
		Negative	Count	1	10	11	
			% within Rapid Urease	9.1%	90.9%	100.0%	
			% within Alcohol	4.2%	38.5%	22.0%	
	Total		Count	24	26	50	
			% within Rapid Urease	48.0%	52.0%	100.0%	
			% within Alcohol	100.0%	100.0%	100.0%	

RAPID UREASE * ALCOHOL * GROUP

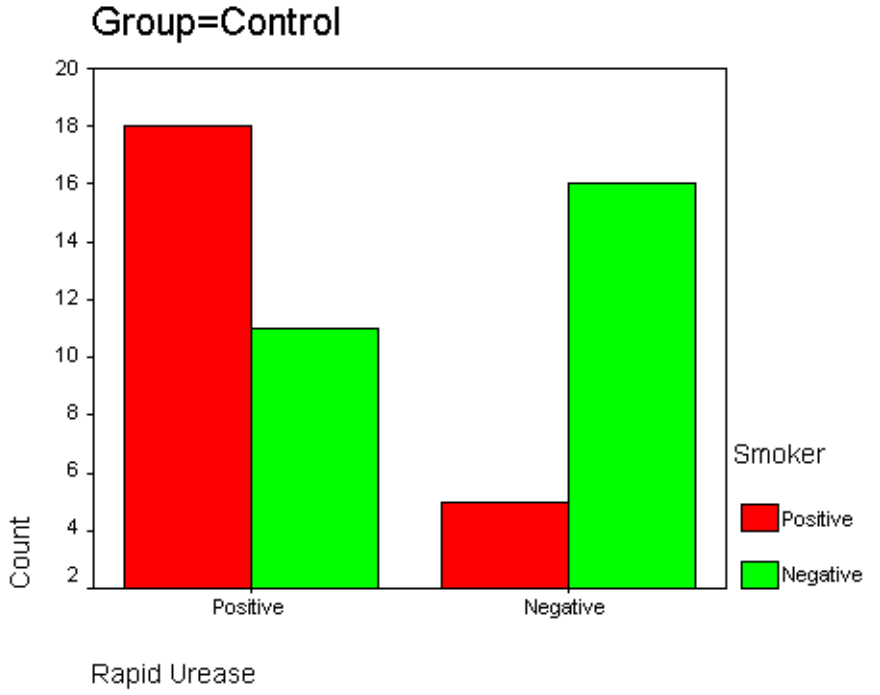


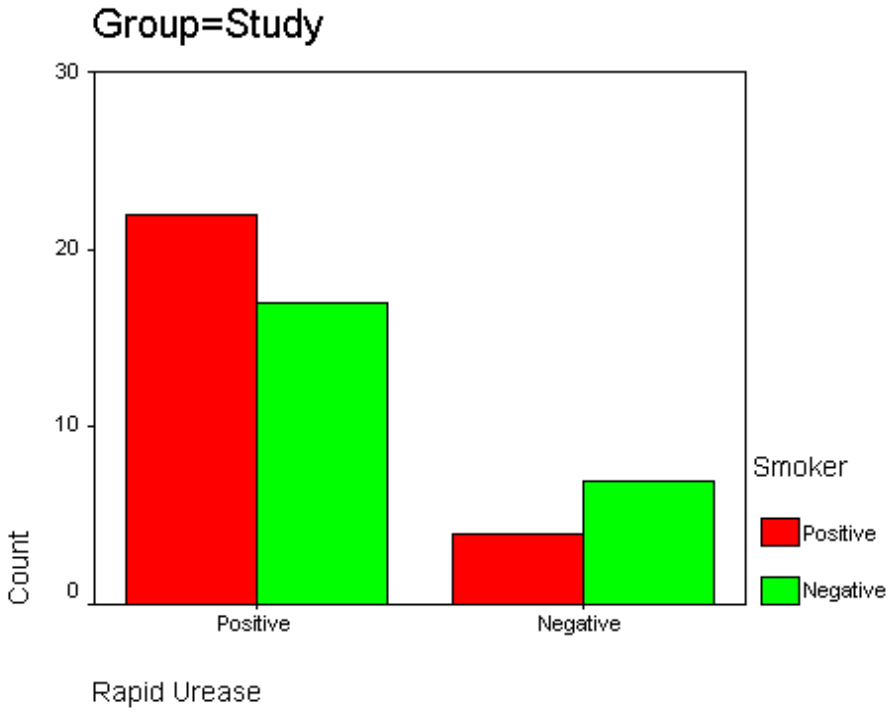


RAPID UREASE * SMOKER * GROUP

Group				Smoker		Total	P value
				Positive	Negative		
Control	Rapid Urease	Positive	Count	18	11	29	0.007**
			% within Rapid Urease	62.1%	37.9%	100.0%	
			% within Smoker	78.3%	40.7%	58.0%	
		Negative	Count	5	16	21	
			% within Rapid Urease	23.8%	76.2%	100.0%	
			% within Smoker	21.7%	59.3%	42.0%	
	Total		Count	23	27	50	
			% within Rapid Urease	46.0%	54.0%	100.0%	
			% within Smoker	100.0%	100.0%	100.0%	
Study	Rapid Urease	Positive	Count	22	17	39	0.240
			% within Rapid Urease	56.4%	43.6%	100.0%	
			% within Smoker	84.6%	70.8%	78.0%	
		Negative	Count	4	7	11	
			% within Rapid Urease	36.4%	63.6%	100.0%	
			% within Smoker	15.4%	29.2%	22.0%	
	Total		Count	26	24	50	
			% within Rapid Urease	52.0%	48.0%	100.0%	
			% within Smoker	100.0%	100.0%	100.0%	

RAPID UREASE * SMOKER * GROUP

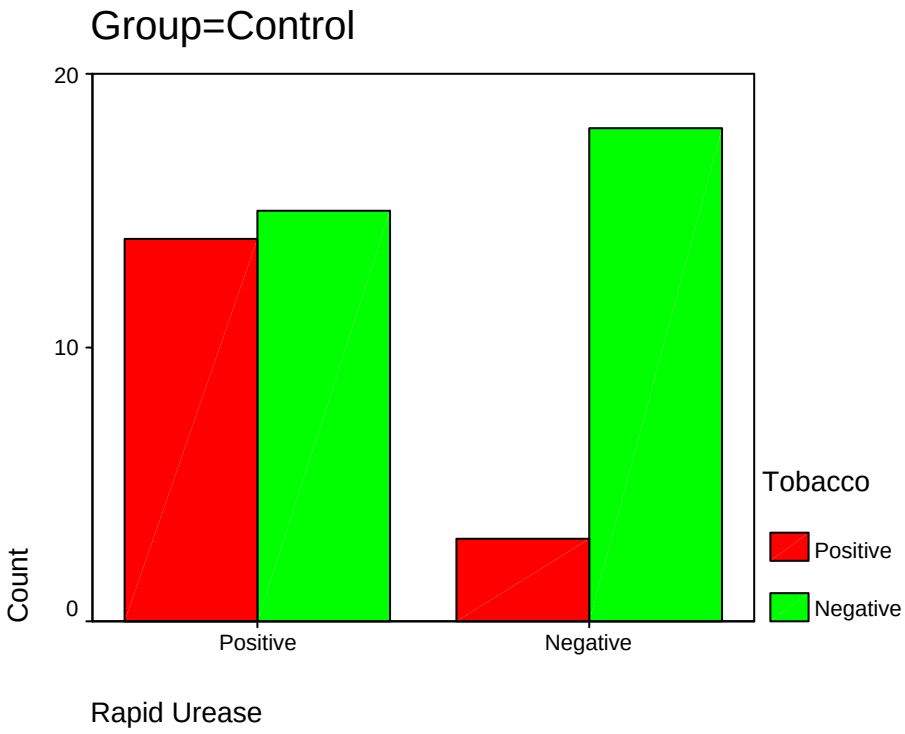


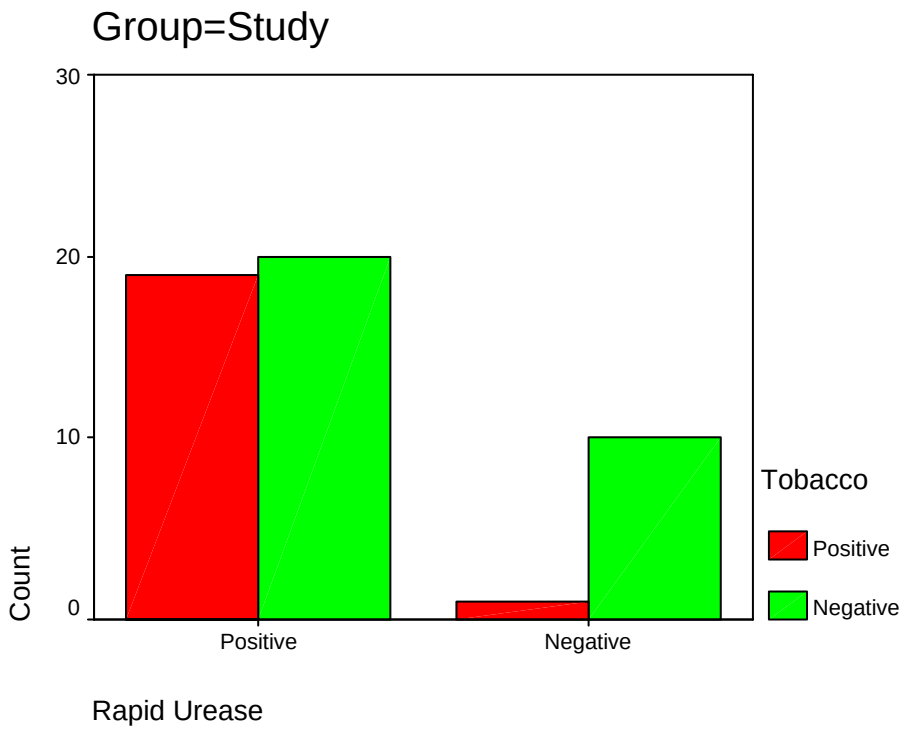


RAPID UREASE * TOBACCO * GROUP

Group				Tobacco		Total	P value
				Positive	Negative		
Control	Rapid Urease	Positive	Count	14	15	29	0.012*
			% within Rapid Urease	48.3%	51.7%	100.0%	
			% within Tobacco	82.4%	45.5%	58.0%	
		Negative	Count	3	18	21	
			% within Rapid Urease	14.3%	85.7%	100.0%	
			% within Tobacco	17.6%	54.5%	42.0%	
	Total		Count	17	33	50	
			% within Rapid Urease	34.0%	66.0%	100.0%	
			% within Tobacco	100.0%	100.0%	100.0%	
Study	Rapid Urease	Positive	Count	19	20	39	0.018*
			% within Rapid Urease	48.7%	51.3%	100.0%	
			% within Tobacco	95.0%	66.7%	78.0%	
		Negative	Count	1	10	11	
			% within Rapid Urease	9.1%	90.9%	100.0%	
			% within Tobacco	5.0%	33.3%	22.0%	
	Total		Count	20	30	50	
			% within Rapid Urease	40.0%	60.0%	100.0%	
			% within Tobacco	100.0%	100.0%	100.0%	

RAPID UREASE * TOBACCO * GROUP





DISCUSSION

DISCUSSION

The main risk factors for the development of gastric cancer are infection with Helicobacter pylori, dietary factors, cigarette smoking, obesity and an inherited predisposition. Considering that relatives of gastric carcinoma patients may be more prone to developing the disease themselves due to familial clustering, the presence of Helicobacter pylori in them may further increase the risk of their developing carcinoma stomach.

Various studies have demonstrated that the first degree relatives of patients with gastric carcinoma are more likely to develop premalignant changes in the stomach and that these changes were mainly seen in persons with associated Helicobacter pylori infection.

Previously conducted studies differ on the prevalence of H.pylori in the general population and first degree relatives of gastric carcinoma patients. Whereas some studies showed an increased prevalence of Helicobacter pylori in the latter group other studies couldn’t find any major difference between the prevalence in both the groups.

Our study found that the prevalence of Helicobacter pylori infection was higher in the study group than that seen in the control

group. The prevalence of Helicobacter pylori was 58% in the control group, whereas it was 78% in the study group. This was found to be statistically significant with a p value of 0.032.

Data obtained from South Korea indicates that persons with a family h/o gastric carcinoma have an increased incidence of not only Helicobacter pylori infection but are also associated with atrophic gastritis or intestinal metaplasia.[5] 185 patients with gastric carcinoma, 130 of their siblings and 287 controls were recruited for this study. Status of Helicobacter pylori infection along with the histological changes was then assessed. Siblings were found to have a higher rate of infection with Helicobacter pylori ($P = 0.046$) and also a higher prevalence of intestinal metaplasia in the body of stomach ($P = 0.027$) when compared with the controls. They concluded that even in young adults, infection with Helicobacter pylori is to be considered a risk factor for gastric carcinoma and those with histopathological findings like corporal gastritis, corporal atrophy or intestinal metaplasia are at an increased risk. As siblings may share common risk factors, all family members should be advised screening.

In our study, premalignant changes as evidenced by atrophic gastritis were present only in the study group. There were no such

changes seen in the control group. But this was statistically not significant (p=0.268) as the incidence of premalignant changes was very less.

In a study conducted by Nasrin Zendehdel MD et al in Iran[6] between 2002 and 2005, 989 subjects who were first degree relatives of gastric carcinoma patients, aged between 40 and 65 years underwent upper GI scopies. After ruling out the presence of any gross lesions in the stomach, five tissue specimens were biopsied and then evaluated according to the Sydney Classification. One specimen was used for urease testing so as to determine the type and severity of the gastritis. They found that only 7% of stomach tissue specimens were normal. Two persons had gastric cancer and one had esophageal cancer. The rest of the persons had premalignant changes with predominant atrophic gastritis and few cases with intestinal dysplasia. They concluded that about one-fifth of the first degree relatives had H.pylori induced corpus-predominant gastritis and that since these people are at increased risk for developing carcinoma stomach, H.pylori eradication is indicated.

In a study by Whiting JL et al in patients with atrophic gastritis or intestinal metaplasia, an 11% increased risk of developing gastric carcinoma was reported when followed up for a period of 10 years.[7]

In our study, what stood out was the fact that all the 4 persons (100%) who showed atrophic gastritis had evidence of Helicobacter pylori infection (as confirmed by a positive rapid urease test).

In our study, there was a slight discordance between the rapid urease test and the histological evidence of Helicobacter pylori in both groups. Only 25 out of the 29 persons in the control group and 34 out of 39 persons in the study group with a positive rapid urease test were able to demonstrate histological evidence of H.pylori. This discordance may be due to the fact that only eosin and hemotoxylin stains were used in the histological examination. Application of special stains such as Modified Giemsa, Silver stains etc., may have aided in accurately detecting Helicobacter pylori. Hence, we may infer that the rapid urease test may be more sensitive for the identification of Helicobacter pylori infection and can be used in the endoscopy suite itself to diagnose and treat Helicobacter pylori.

All persons in our study with a positive rapid urease test were treated as a case of Helicobacter pylori infection and were put on triple therapy with two antibiotics (amoxicillin and clarithromycin) and a PPI.

Wong et al were the first to conduct and publish a prospective RCT that looked into the effect of eradication of Helicobacter pylori on the

development of gastric carcinoma in 2004.[8] They randomized 1630 persons from a high-risk region in China with confirmed H. pylori infection to either receive eradication therapy or placebo. Following these persons for 7.5 years, there was no significant difference in the development of gastric carcinoma between the two groups (7 vs11 cases, P= 0.33). But, a detailed subgroup analysis demonstrated a significant benefit (P = 0.02) from eradication of H.pylori in persons who didn't have intestinal metaplasia at the time of enrollment in this study.

There are no clear guidelines regarding surveillance in cases with premalignant changes in the stomach.

ASGE guidelines

The ASGE guidelines for gastric intestinal metaplasia are:

- Endoscopic surveillance for gastric intestinal metaplasia can't be uniformly recommended as this entity hasn't been studied extensively in the USA.
- Patients who have an increased risk for gastric carcinoma due to ethnic background or family history may benefit from surveillance.
- Endoscopic surveillance should incorporate topographic mapping of the entire stomach.

Unfortunately, there are no randomized studies comparing different strategies in this situation, with endoscopic control performed yearly, every 2 years or less frequently in various centers. But, in a UK study with a yearly endoscopic control, 36% of detected gastric cancers were stage I disease, a rate which would appear similar to the 38% achieved in Italy with a 2-year endoscopic control.[9]

The Annual Symposium of the Korean College of Helicobacter and Upper Gastrointestinal Research asked its members to discuss, vote and recommend screening strategies for premalignant changes in stomach. These recommendations were published in the March 2012 issue of the Digestive Diseases & Sciences Vol. 57 Issue 3, p746. The commonly recommended suggestion for persons with intestinal metaplasia was to have an annual endoscopic follow-up (95.5% vs. 80.4% in the expert and non-expert groups, respectively; P = 0.118). The same follow-up was also recommended for those with atrophic gastritis (95.5% vs. 76.5%; P = 0.092). This was irrespective of the physicians' endoscopic experience, position and type of the hospital.

In another study by Angelo Zullo et al published in World J Gastrointest Oncol. 2012 March 15; 4(3): 30–36, reported that *H. pylori* eradication may slow intestinal metaplasia progression, scheduled

endoscopic control could be cost-effective in intestinal metaplasia patients and that yearly and 2 yearly controls seem to be equally effective but specific studies are needed in this setting.

The persons in the study group with atrophic gastritis were advised to have an annual surveillance upper GI scopy. This was advised to monitor the patient and detect gastric carcinoma (if it occurs) at an early stage as there is a better 5 year survival rate when the disease is identified earlier on.

However, larger multicenter randomized control trials across countries are needed to find out the potential benefits of such a surveillance programme and whether their application will vary in regions with low incidence from those that have a high incidence of gastric cancer.

CONCLUSION

CONCLUSION

- This study shows that the prevalence of Helicobacter pylori is higher in first degree relatives of patients with gastric carcinoma than that seen in the control group.
- The presence of premalignant changes (atrophic gastritis) was seen only in a few persons in the the study group.
- Premalignant changes were seen only in persons who showed the presence of Helicobacter pylori as evidenced by the presence of a positive rapid urease test and positive histological examination.
- Rapid urease test was slightly more sensitive than histological examination in the detection of H.pylori.
- This study showed a positive correlation between alcohol intake and tobacco chewing with the prevalence of H.pylori, whereas there was an inconsistent correlation between smoking and H.pylori.

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ANNEXURES

PROFORMA

NAME:

AGE: SEX: OCCUPATION:
SOCIO-ECONOMIC STATUS:

ADDRESS:

DDHD NUMBER:

PRESENTING COMPLAINTS:

RELEVANT HISTORY:

HISTORY OF PUD:
HISTORY OF GASTRECTOMY:

HISTORY OF ALCOHOLISM:

HISTORY OF SMOKING/ TOBACCO/SNUFF:

HISTORY OF EXPOSURE TO STD:

HISTORY OF OTHER COMORBID CONDITIONS:

GENERAL EXAMINATION:

PALLOR: , ICTERUS: ,CLUBBING: , CYANOSIS: ,PEDAL EDEMA: , LYMPHADENOPATHY(GENERAL AND LT. SUBCLAVIAN) :

HEIGHT: WEIGHT: BMI:

JVP: TEMPERATURE: PULSE:
BLOOD PRESSURE:

EXAMINATION OF THE ABDOMEN:

MASS ABDOMEN:

HEPATOMEGALY:

ASCITES: VGP:
SUCCUSSION SPLASH:

PER RECTAL EXAM:

EXAMINATION OF THE CARDIOVASCULAR SYSTEM:

EXAMINATION OF THE RESPIRATORY SYSTEM:

EXAMINATION OF THE NERVOUS SYSTEM:

DIAGNOSIS:

INVESTIGATIONS

COMPLETE HEMOGRAM:

HEMOGLOBIN: TOTAL COUNT: DIFFERENTIAL COUNT: P L B E M

PLATELET COUNT: ESR:

BLOOD SUGAR: BLOOD UREA: SERUM CREATININE:

STOOL OCCULT BLOOD: XRAY CHEST:

ULTRASONOGRAPHY ABDOMEN:

OGD SCOPY FINDINGS:

RAPID UREASE TEST:

HISTOPATHOLOGICAL EXAMINATION FINDINGS:

MASTER CHART

STUDY GROUP

Sl.No	NAME	DDHD NUMBER	AGE	SEX	SMOKER	ALCOHOL	TOBACCO	RAPID UREASE	HISTOLOGY FOR H.PYLORI	ATROPHIC GASTRITIS	INTESTINAL METAPLASIA	DYSPLASIA
1	GIRIJA	6381/12	48	F	N	N	N	N	N	N	N	N
2	MAHALAKSHMI	6630/12	20	F	N	N	N	P	N	N	N	N
3	MUTHURAMAN	7304/12	40	M	P	P	P	N	N	N	N	N
4	THAMARAISELVAN	7305/12	35	M	P	P	N	P	P	N	N	N
5	SELVI	7670/12	23	F	N	N	N	P	P	N	N	N
6	THANGAMALAR	5034/12	35	F	N	N	P	P	P	N	N	N
7	DHARMALINGAM	1265/12	33	M	P	P	P	P	P	N	N	N
8	PARTHIBAN	8000/12	22	M	N	P	N	P	P	N	N	N
9	ISAKKIPANDIAN	758/13	34	M	P	P	P	P	P	N	N	N
10	DHANASEKHAR	7169/12	43	M	P	N	N	N	N	N	N	N
11	MUNUSAMY	7790/12	30	M	P	P	N	P	P	N	N	N
12	NOOR JAHAN	7296/12	48	F	N	N	P	P	N	N	N	N
13	MOHD.ISMAIL	7599/12	19	M	N	N	N	P	P	N	N	N
14	GEETHA	6323/12	42	F	N	N	P	P	P	P	N	N
15	MEENAVATHY	7081/12	45	F	N	N	N	P	P	N	N	N
16	VISWANATHAN	5911/12	56	M	P	P	P	P	P	P	N	N
17	VIJAYA	6774/12	50	F	N	N	P	P	P	N	N	N
18	YUVARAJ	6658/12	35	M	P	P	P	P	P	N	N	N
19	MOHAN	7184/12	28	M	P	P	N	P	N	N	N	N

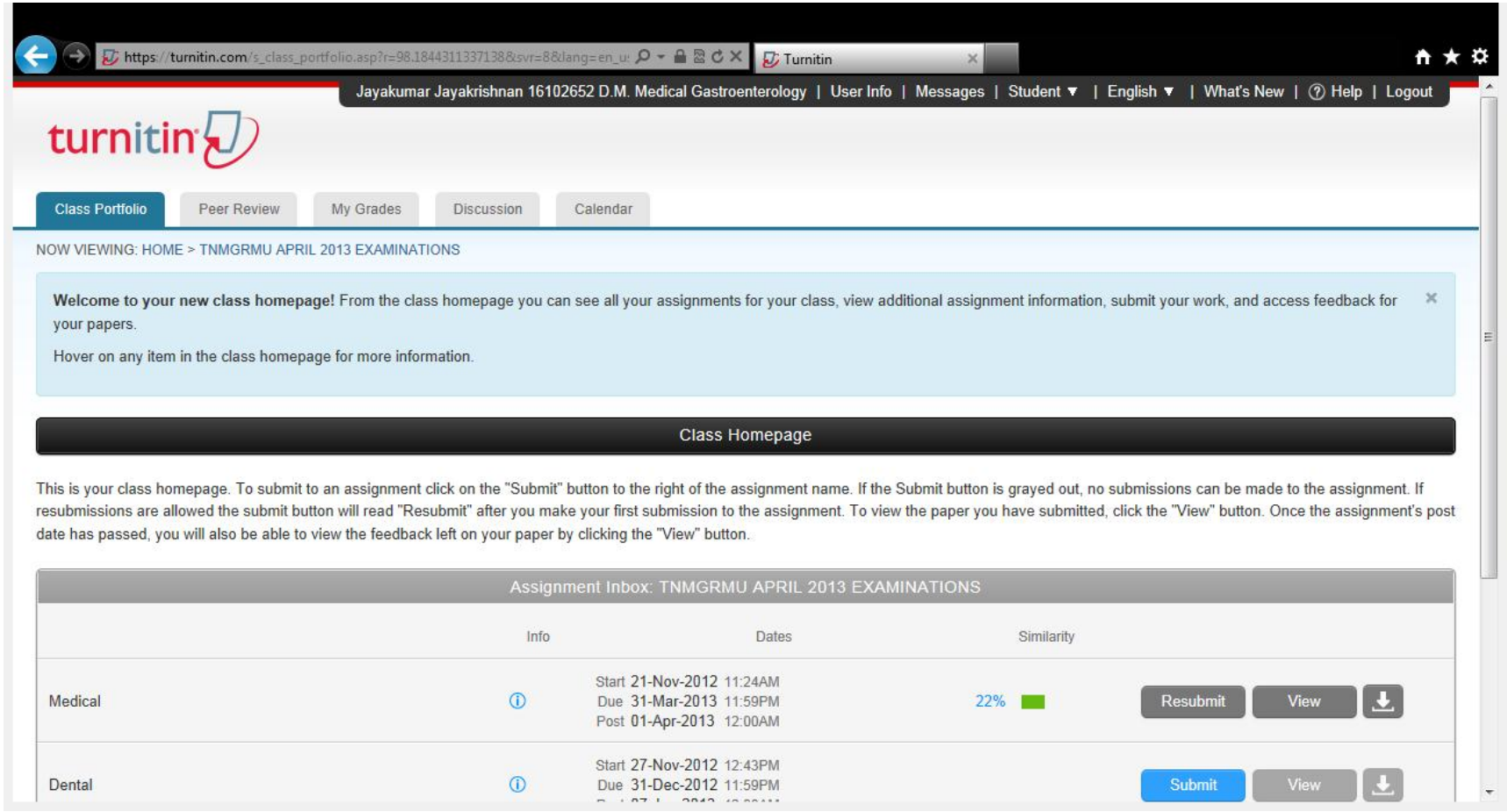
20	GOVINDAN	7798/12	48	M	P	N	N	N	N	N	N	N
21	KRISHNAN	5911/12	56	M	N	P	P	P	P	P	N	N
22	PALANISAMY	3414/08	29	M	P	P	N	P	P	N	N	N
23	VEDAGIRI	4110/12	55	M	P	P	P	P	P	N	N	N
24	NITHYA	7736/12	14	F	N	N	N	N	N	N	N	N
25	VELU	3414/08	29	M	P	P	N	P	P	N	N	N
26	BALAKRISHNAN	7742/12	35	M	P	P	P	P	P	N	N	N
27	JEYASHREE	5988/12	28	F	N	N	N	N	N	N	N	N
28	PANEERSELVAM	7834/12	25	M	P	P	N	P	P	N	N	N
29	JEYASUDHA	1177/09	26	F	N	N	N	P	P	N	N	N
30	NAGARAJAN	7902/12	42	M	P	P	P	P	P	P	N	N
31	VENKATESAN	5623/09	35	M	P	P	N	P	P	N	N	N
32	PUSHPA	1314/13	34	F	N	N	N	N	N	N	N	N
33	SRIRAM	7883/12	40	M	P	P	P	P	P	N	N	N
34	NETHAJI	8071/12	60	M	N	N	N	N	N	N	N	N
35	LAKSHMI	7510/12	33	F	N	N	N	P	P	N	N	N
36	VISALAKSHI	184/13	25	F	N	N	N	P	P	N	N	N
37	SHANKAR	33/13	39	M	P	P	N	P	N	N	N	N
38	PETCHIAMMAL	8200/12	33	F	N	N	P	P	P	N	N	N
39	CHINNA REDDY	349/13	41	M	P	P	P	P	P	N	N	N
40	VEERA PRASANNA	1460/13	25	M	P	P	N	P	P	N	N	N
41	RAMACHANDRA	6465/12	18	M	N	N	N	N	N	N	N	N
42	SELVAM	7685/12	37	M	P	P	P	P	P	N	N	N
43	RANI	5277/12	35	F	N	N	P	P	P	N	N	N

44	NATARAJAN	3310/12	34	M	P	P	P	P	P	N	N	N
45	SHANKAR	79/13	38	M	P	N	N	N	N	N	N	N
46	PETCHIAMMAL	8178/12	32	F	N	N	N	P	P	N	N	N
47	SUMATHI	298/13	44	F	N	N	P	P	P	N	N	N
48	LAKSHMI	267/13	55	F	N	N	N	N	N	N	N	N
49	KESAVAN	1685/12	31	M	P	P	N	P	P	N	N	N
50	CHAKRAVARTHI	661/13	25	M	P	N	N	P	N	N	N	N

Control Group

1	ISAAC	7379/12	29	M	P	P	P	P	P	N	N	N
2	RAJESWARI	7655/12	46	F	N	N	P	P	P	N	N	N
3	KOKILA	5790/12	36	F	N	N	N	N	N	N	N	N
4	RAJKUMAR	7710/12	19	M	N	P	N	N	N	N	N	N
5	SUNDAR	225/11	53	M	P	P	P	P	P	N	N	N
6	ARASU	7814/12	31	M	P	N	N	N	N	N	N	N
7	DAMAYANTHI	5514/12	33	F	N	N	N	N	N	N	N	N
8	MARY	7873/12	46	F	N	N	P	P	P	N	N	N
9	RAJU	7969/12	27	M	P	P	N	P	P	N	N	N
10	MURUGAN	7966/12	21	M	P	P	N	P	N	N	N	N
11	THIRAVIDAMANI	7917/12	30	M	P	N	N	N	N	N	N	N
12	VASUKI	8077/12	40	F	N	N	N	P	P	N	N	N
13	RAMESH	4210/12	33	M	P	P	N	P	P	N	N	N
14	ARULPRAKASAM	8074/12	30	M	P	P	N	P	P	N	N	N
15	MOORTHY	8106/12	30	M	N	N	P	N	N	N	N	N
16	SHANTHI	8127/12	45	F	N	N	P	P	P	N	N	N
17	VINOTH	8021/12	23	M	N	N	N	N	N	N	N	N
18	KARPAGAM	8072/12	32	F	N	N	N	N	N	N	N	N
19	LAKSHMI	48/13	37	F	N	N	N	N	N	N	N	N
20	JAYAKUMAR	5717/11	43	M	P	P	N	P	P	N	N	N
21	AMUDHAVALLI	8011/11	30	F	N	N	N	N	N	N	N	N
22	UMAPATHY	121/13	35	M	P	P	N	P	P	N	N	N
23	LAKSHMI	148/13	47	F	N	N	P	P	P	N	N	N
24	MUNIAPPAN	176/13	23	M	N	P	N	N	N	N	N	N
25	JEYARAMAN	193/13	53	M	P	P	P	P	P	N	N	N
26	NEELAM DEVI	7928/12	35	F	N	N	N	P	P	N	N	N
27	RAVI	3132/12	45	M	P	P	N	P	P	N	N	N

28	VASANTHA	329/13	56	F	N	N	P	P	P	N	N	N
29	KAMARAJ	335/13	41	M	P	P	N	P	P	N	N	N
30	JEYARAJAN	4748/10	40	M	P	P	P	P	P	N	N	N
31	GOVINDASAMY	458/13	28	M	P	P	N	P	N	N	N	N
32	RAJAN	460/13	37	M	P	P	P	P	P	N	N	N
33	ROBERT	443/13	35	M	P	P	N	N	N	N	N	N
34	KALYANI	450/13	52	F	N	N	P	P	P	N	N	N
35	KASTHURI	563/13	45	F	N	N	N	N	N	N	N	N
36	MOHANRAJ	482/13	42	M	P	N	N	P	P	N	N	N
37	SELVI	597/13	27	F	N	N	N	N	N	N	N	N
38	ROHINI	6125/04	38	F	N	N	N	P	N	N	N	N
39	KUMAR	552/13	34	M	N	P	N	N	N	N	N	N
40	BAKRUDEEN	6540/09	50	M	P	P	P	P	P	N	N	N
41	RUKMANI	403/13	65	F	N	N	P	P	P	N	N	N
42	LAKSHMI	4354/11	15	F	N	N	N	N	N	N	N	N
43	RAJINI	5261/12	26	M	P	N	N	N	N	N	N	N
44	KARUNANIDHI	775/13	21	M	N	P	P	N	N	N	N	N
45	UMA	712/13	30	F	N	N	N	N	N	N	N	N
46	SUNDARAM	809/13	48	M	P	P	N	P	P	N	N	N
47	GOKUL	813/13	16	M	P	N	N	N	N	N	N	N
48	BHARATHY	915/13	53	F	N	N	P	P	P	N	N	N
49	RAMESH	779/13	30	M	P	N	N	P	N	N	N	N
50	SELVAKUMAR	908/13	26	M	N	N	P	N	N	N	N	N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